REMARKS

Applicant acknowledges the withdrawal of the earlier rejection of claims 1-4 under 35 USC 103(a) as being unpatentable over Sanchez-Ramos et al. (2000, Exp. Neurology, Vol. 164, pgs. 247-256), Inoue et al. (2001, Genes to Cells, Vol. 6, pgs. 977-986) and Elwood et al. (1998, Blood, Vol. 91, pgs. 3756-3765).

The Examiner has now replaced the rejection which has been withdrawn with a new rejection of claims 1, 2, 5 and 6, under 35 USC 103(a) as being unpatentable over Woodbury et al (2000, J. Neuroscience Res. Col 61, pgs 364-370) and Guillemot F. (1999, Experimental Cell Res., Vol. 253, pgs. 357-364). This rejection is respectfully traversed.

Claim 1 is limited to a method for transdifferentiating mesenchymal stem cells into neuronal cells, which comprises increasing the level of a basic helix-loop-helix (bHLH) transcription factor in the mesenchymal stem cells.

The technical feature of the subject invention relates to transdifferentiating mesenchymal stem cells (MSC) into neuronal cells by increasing the level of a basic helix-loop-helix (bHLH) transcription factor in the MSCs. The subject invention as claimed is completely different from the several methods known to the prior art for inducing differentiation of mesenchymal stem cells (MSCs) into neuron-like cells, e.g., by culturing MSCs in the presence of growth factors or homones such as EGF or BDNF as is taught in the "Background of the Invention" on page 1 lines 24-29.

As indicated by the Examiner in his Office Action, none of the cited references, i.e., Woodbury et al. and Guillemot, teaches the technical feature of the subject invention of transdifferentiating the MSCs by increasing the level of a basic helix-loop-helix (bHLH) transcription factor in the MSCs. Moreover, if the cited references are combined, such technical feature is not obvious.

More specifically, Woodbury et al. discloses that bone marrow stromal cells (BMSCs) can be induced to differentiate into neural cells by culturing the BMSCs in neuronal induction media, containing either DMEM/1-10mM β-mercaptoethalnol or DMEM/2% dimethylsulfoxide (DMSO)/200μM butylated hydroxyanisole (BHA), which is not a bHLH transcription factor.

Further, although Woodbury et al. discloses that BMSCs cultured in said media exhibited a neuronal phenotype by expressing neuron-specific enolase, NeuN, neurofilament-M and tau, recent studies have indicated that the identification of such proteins is not sufficient or might be even incorrect to confirm the differentiation into neural cells, as discussed hereinafter.

In addition, Guillemot merely discloses a role of a bHLH transcription factor in differentiation of neuronal progenitor cells, **not** MSCs, into neuronal cells. In this regard, Guillemot states on page 361, 2nd column, 1st paragraph, as follows:

> These results suggest that, by controlling the ability of neuronal progenitors to respond to extrinsic factors, bHLH proteins may play an important role in integrating signals from the environment into transcriptional programs of differentiation.

Also, Guillemot indicates on page 359, 2nd column, 2nd paragraph that bHLH genes interact with Notch signaling in neuronal progenitors to participate in differentiation of the neuronal progenitors.

Accordingly, Guillemot merely deals with a function of bHLH proteins or genes in differentiation of "neuronal progenitors", and does not teach or suggest transdifferentiation of MSCs, whose developmental linage is totally different from that of neuronal progenitors, into neurons.

Therefore, although the bHLH proteins were known in the art by Guillemot, the technical idea that bHLH transcription factors are employed to transdifferentiate MSCs into neuronal cells was not known at the time of filing of the subject application.

In addition, since none of the cited references teach or suggest the critical technical feature of the subject invention, i.e., the use of bHLH transcription factors for transdifferentiating the MSCs into neuronal cells, those skilled in the art would have no basis for using the combination of the cited references as suggested by the Examiner, without the aid of hindsight.

Recent studies have found that the method of identifying the differentiation of BMSCs into neuron-like cells employed in Woodbury et al. is not sufficient or may be even incorrect to confirm the differentiation of MSCs into neuronal cells since morphological change into neuron-like morphology and increases in immunolabeling for certain neuronal markers such as NSE

and NeuN are not the result of genuine neuronal differentiation but represent cellular responses to chemical stress (*see the* Abstract, in Exhibit 1 attached to applicants response filed September 9, 2008, on page 185, and note that Exhibit 1 directly cites Woodbury et al. on page 175, left column, 3rd line and in the Results).

Further, in the Abstract of Neuhuber et al. in Exhibit 5, attached to applicants response filed September 9, 2008, reported that "a dissection of molecular signaling and commitment events may be necessary to verify the ability of MSC transdifferentiation to neuronal linages," while mentioning Woodbury et al. as one of in vitro differentiation protocols leading to unexpected, misleading results.

Accordingly, it cannot be said that MSCs were differentiated into neuronal cells without demonstrating eletrophysiological properties of differentiated MSCs. In this connection, the subject invention has demonstrated that MSCs expressing bHLH transcription factor not only express neuron-specific proteins but also have electrophysiological properties (*see* Example 4, page 10 of the subject specification).

In a developmental process, neuronal precursor cells or neuronal stem cells, which are committed to be differentiated into a neuron, are derived from ectoderm, while MSCs, which are committed to be differentiated into bone cells, cartilage cells and the like, are derived from mesoderm. Therefore, the differentiation potential of MSCs is quite different from that of neuronal progenitor

cells or neuronal stem cells. Accordingly, it is not obvious to transdifferentiate MSCs, which have an embryologically different differentiation potential as compared with neuronal precursor cells or neuronal stem cells, into neuronal cells by expressing therein a certain bHLH transcription factor. This is also supported by Paul Lu et al. in Exhibit No. 4, attached to applicants response filed September 9, 2008, describing that 'transdifferentiation' is a rare phenomenon and is not readily explainable in terms of normal developmental process (*see* page 175, right column, second paragraph). An IDS is attached hereto to make of record the Exhibits 1-5 as attached to applicants response filed September 9, 2008.

For all of the above reasons, the rejection of claims 1, 2, 5 and 6 under 35 USC 103(a) should be withdrawn.

The rejection of claims 3 and 4 under 35 USC 103(a) as being unpatentable over Woodbury et al and Guillemot as applied to claims 1, 2, 5 and 6 in combination with Ellwood et al is respectively traversed for the same reasons as given above in combination with claims 1, 2, 5 and 6, since claims 3 and 4 are dependent claims.

Moreover, Ellwood et al does not teach or suggest the method of claim 1 and therefore provides no teaching to support the rejection of claims 1, 2, 5 and 6 in combination with Woodbury and Guillemot.

The rejection of claim 8 under 35 USC 103(a) as being unpatentable over Woodbury et al and Guillemot as applied to claims 1, 2, 5 and 6 in combination with Zou et al (2002, J. Neuroscience, Vol. 22 (12), pgs. 4833-4841), is respectfully

traversed for the same reasons as given above. Claim 8 is also a dependent claim and Zou et al does not teach or suggest the method of claim 1.

Applicant acknowledges that claim 7 contains allowable subject matter which will be allowable if converted into an independent claim to include all of the limitations of the base claim and any intervening claims.

Reconsideration and allowance of claims 1-8 is respectfully solicited.

Respectfully submitted,

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CERTIFICATE OF TRANSMISSION

I hereby certify that this Response w/attachments is being submitted to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 via EFS-Web on April 28, 2009.

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L. Quagliariello